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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/516,744

12/06/2004

Eric Trinquet

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EXAMINER

STAPLES, MARK

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

01/22/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,744	TRINQUET ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/15/2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42-64 is/are rejected.
- 7) ☒ Claim(s) 61 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/ are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/15/2007</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

1. Applicant's cancellation of claims 1-41 and submission of new claims 42-64 in the paper filed on 11/15/2007 is acknowledged.

Claims 42-64 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn / Moot

Specification

2. The objection to the specification for improper use of the trademark BODIPY® is withdrawn in light of Applicant's amendment of this trademark.

Claim Objection Moot

3. The objection to claim 18 is moot in light of Applicant's cancellation of this claim.

Claim Rejections Moot - 35 USC § 112 Second Paragraph

4. The rejections of claims 1-6 and 14-30 under 35 USC § 112 Second Paragraph are moot in light of Applicant's cancellation of these claims.

Claim Rejections Moot - 35 USC § 102(b)

5. The rejections of claims 1-6, 14, 15, and 17-24 under 35 USC § 102(b) are moot in light of Applicant's cancellation of these claims.

Claim Rejections Moot - 35 USC § 103(a)

6. The rejections of claims 16 and 25 under 35 USC § 103(a) are moot in light of Applicant's cancellation of these claims.

Sequence Rules Compliance

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

As Applicant has explained in remarks filed 10/11/2007 claim 61 contains a sequence of 15 nucleotides. The sequence of claim 61 does not have a SEQ ID NO.

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Also Pages 24-37 and 39-41 respectively contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provided by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in a sequence listing, Applicant should provide a substitute sequence listing and a CRF that include those sequences.

New Objections and Rejections Necessitated by Amendment

New Claim Objection

8. Claim 61 is objected to because of the following informalities: Claim 61 recites a nucleic acid sequence without the corresponding SEQ ID NO. Appropriate correction is required. See also Sequence Rules Compliance above and attached Notice to Comply.

New Claim Rejections - 35 USC § 102

9. Claims 42-44, 46, 47, 51-56, 59-61, 64, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Tyagi et al. (US Patent No. 5,925,517 issued 1999).

Regarding claims 42, 55, 56, 60, and 61 Tyagi et al. teach a fluorescent conjugate comprising:

- a fluorescent entity covalently attached to one or more oligonucleotides (entire patent, especially claims 1, 6, and 13)

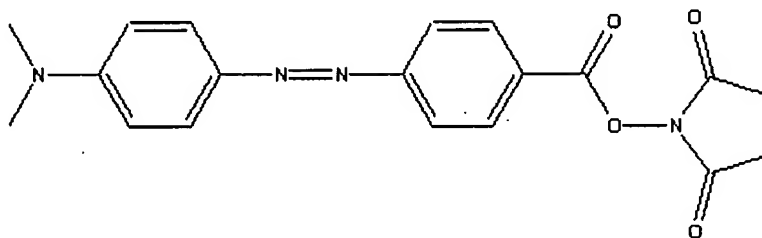
- a carrier molecule which is an antibody which is a type of protein (the antibody here interpreted as the carrier molecule, see Figure 1 and its detailed description found at column 9 line 2 through to column 11 line 21).

said entity being covalently attached through the functional group of hydroxysuccinimide ester on the fluorophore by teaching the fluorophore which is the succinimidyl ester of DABCYL (Molecular Probes, Eugene, Oregon, see column 26, line 51 and 52). It is noted that the succinimidyl ester of DABCYL is a N-hydroxysuccinimide as seen in the structure given in Figure 1 below.

Figure 1

DABCYL, SE

[4 - ((4 - (dimethylamino)phenyl)azo)benzoic acid, succinimidyl ester]



Retrieved on 01/16/2008 from:

<http://www.anaspec.com/products/product.asp?id=28921>

Regarding claims 43, 50, and 63, Tyagi et al. teach an oligonucleotide of 3 to 15 nucleotides in length which is within the range of 2 to 60 nucleotides in length (see claim 8).

Regarding claims 44 and 47, Tyagi et al. teach where the fluorophore is attached via a spacer arm (see claims 22 and 110).

Regarding claim 46, Tyagi et al. teach fluorescein and sulforhodamine which is a type of rhodamine (see column 16 line 41-59).

Regarding claims 51-54, Tyagi et al. teach: "Hybridization probes of the invention can be made from DNA, RNA, or some combination of the two. The probes may include modified nucleotides. Modified internucleotide linkages are useful in probes comprising deoxyribonucleotides and ribonucleotides to alter, for example, hybridization strength and resistance to non-specific degradation and nucleases. The links between nucleotides in the probes may include bonds other than phosphodiester bonds, for example, peptide bonds. Modified internucleotide linkages are well known in the art and include methylphosphonates, phosphorothioates, phosphorodithionates, phosphoroamidites and phosphate ester linkages" (see column 8 line 65 continuing to column 9 line 10).

Regarding claims 59 and 64, Tyagi et al. inherently teach a molar ratio of at least 1 (entire patent) The molar ratio is interpreted to be the molar ratio of the fluorophore-nucleotide conjugate to the antibody. By definition, this molar ratio must be at least 1, as at least one fluorophore-nucleotide conjugate molecule must be covalently linked to at least one antibody molecule. Tyagi et al. thus inherently teach a molar ratio of at least 1.

10. Claims 45, 48, 57, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al. as applied to claim 42 and 47 above, and further in view of Glazer et al. (US Patent No. 5,853,992 issued 1998).

Tyagi et al. teach noted above.

Regarding claims 45 and 62, Tyagi et al. do inherently teach where the fluorophore has aromatic rings (see Figure 1 above).

Regarding claims 45 and 62, Tyagi et al. do not specifically teach molar extinction coefficient of greater than $20,000 \text{ M}^{-1} \text{ cm}^{-1}$ or greater than $50,000 \text{ M}^{-1} \text{ cm}$ and regarding claims 48 and 57 Tyagi et al. do not specifically teach divalent spacer arms.

Regarding claim 45 and 62, Glazer et al. teach where the fluorophore has aromatic rings and has a molar extinction coefficient of greater than $60,000 \text{ M}^{-1} \text{ cm}^{-1}$ (see column 3 lines 9-38).

Regarding claim 48 and 57, Glazer et al. teach a linear alkylene spacer arm having a divalent organic radical which can be of the length of $\text{C}_1\text{-C}_{20}$ and containing one hetero atom, N (see the structure at column 8, lines 14-22 and see claim 27).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the spacer arm of Tyagi et al. by substituting a linear alkylene spacer arm having a divalent organic radical as suggested by Glazer et al. with a reasonable expectation of success. The motivation to do so is provided by Glazer et al. who teach the 20 atom length specifically for use with oligonucleotides: "Linkage of the fluorophores to the backbone is achieved by conventional covalent binding. . . . In the case of nucleic acid backbones

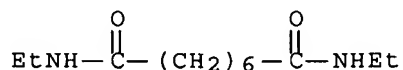
[oligonucleotides], linkage is preferably achieved by use of a convenient linking arm usually consisting of from about 2 to about 20 . . . atoms" (see column 7 line 65 through to column 8 line 9). Glazer et al. further teach: "A preferred linking group structure is an amide-containing chain . . . (see column 8 lines 10-111). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

11. Claims 49 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al. and Glazer et al. as applied to claims 48 and 57 above, and further in view of Surrey et al. (US Patent 3,143,566 issued 1964).

Tyagi et al. and Glazer et al teach as noted above.

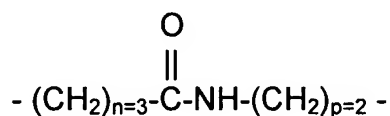
Tyagi et al. and Glazer et al. do not specifically teach a spacer arm of the structures given in claims 49 and 58.

Surrey et al. specifically teach structure 3 of claims 16 and 25 by teaching alkyl diamides and specifically where n=2 in structure 3, Surrey et al. teach N,N'-diethyl octanediamide, CAS Registry No. 91565-14-9, as shown below:



Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the spacer arm of Tyagi et al. and Glazer et al by using N,N'-diethyl octanediamide which is a 20 atom linking arm as suggested by Surrey et al. with a reasonable expectation of success. The motivation to

do so is provided by Glazer et al. who teach the 20 atom length specifically for use with oligonucleotides: "Linkage of the fluorophores to the backbone is achieved by conventional covalent binding. . . . In the case of nucleic acid backbones [oligonucleotides], linkage is preferably achieved by use of a convenient linking arm usually consisting of from about 2 to about 20 . . . atoms" (see column 7 line 65 through to column 8 line 9). Glazer et al. further teach: "A preferred linking group structure is an amide-containing chain . . . (see column 8 lines 10-111). Glazer et al. then teach the exact half of N,N'-diethyl octanediamide by teaching the structure:



which is N ethyl butanamide (see column 8 lines 14-22). It is noted that combining two of these to achieve the 20 atom length gives the structure of Surrey et al. Glazer et al. also teach where there are two amide groups in a linear spacer arm (see Figure 1). From the teachings of Glazer et al. one would be motivated to use various spacer arms of 20 atoms, preferably those including amide groups, and thus preferably including the specific and known one taught by Surrey et al. Thus the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

12. No claim is free of the prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
Examiner
Art Unit 1637
January 15, 2008

MS


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/17/08

Notice to Comply	Application No. 10/516,744	Applicant(s) TRINQUET ET AL.	
	Examiner Mark Staples	Art Unit 1637	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.
- ☒ 7. Other: See Office Action.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923

For CRF Submission Help, call (703) 308-4212 or 308-2923

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